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Vaccination for preventing postherpetic neuralgia (Review)

Chen N, Li Q, Zhang Y, Zhou M, Zhou D, He L

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[Intervention Review]

Vaccination for preventing postherpetic neuralgia

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ABSTRACT

Background

Herpes zoster virus vaccine was recommended for the prevention of herpes zoster and its sequelae by the Advisory Committee on Immunization Practices (ACIP) in 2006. To date the efficacy and safety of vaccination for preventing the most common complication of zoster, postherpetic neuralgia, has not been systematically reviewed.

Objectives

To assess the efficacy and safety of vaccination in preventing postherpetic neuralgia.

Search methods

We searched the Cochrane Neuromuscular Disease Group Specialized Register (10 January 2011), the Cochrane Central Register of Controlled Trials (CENTRAL) Issue 4, 2010 in the *Cochrane Library*), MEDLINE (January 1966 to December 2010), EMBASE (January 1980 to January 2011), LILACS (January 1982 to December 2010), and the Chinese Biomedical Retrieval System (January 1978 to December 2010). We also checked the references of published studies to identify additional trials.

Selection criteria

We included all randomised controlled trials comparing varicella zoster virus vaccination with placebo, no vaccination or another intervention, irrespective of publication status or language.

Data collection and analysis

Two authors independently assessed trial quality, then extracted and analysed data from the trials which met the inclusion criteria. We collected adverse effects information from the trials.

Main results

One trial, which involved 38,546 subjects and compared vaccination with placebo, met our inclusion criteria. This included study was of high quality. However, its participants were all aged 60 years or more and most of them were white, which may mean that its findings are not applicable to all populations. The vaccine was effective in decreasing the incidence of herpes zoster, but there was no evidence that it had efficacy in reducing the incidence of postherpetic neuralgia beyond its effect on the incidence of herpes zoster. Adverse events at the injection site were more common among vaccine recipients than placebo recipients, but they were mild and resolved in a few days. Serious adverse events were rare.

Authors' conclusions

There is insufficient direct evidence from specialised trials to prove the efficacy of vaccine for preventing postherpetic neuralgia beyond its effect on reducing herpes zoster, although vaccination may be efficacious and safe for preventing herpes zoster and thus reduce the incidence of postherpetic neuralgia in adults aged 60 years or older.

PLAIN LANGUAGE SUMMARY

Vaccination for preventing postherpetic neuralgia

Postherpetic neuralgia is a painful condition that occurs in patients after they have been affected by a recurrence of the herpes zoster virus (shingles). The pain may persist for years and is often difficult to treat. Herpes zoster virus vaccination is a possible new approach to prevent herpes zoster and postherpetic neuralgia. We identified a single high quality trial with a total of 38,546 participants, comparing vaccination with placebo. It found a significant reduction of herpes zoster, but did not provide enough direct evidence to draw any conclusion about whether the vaccine is effective in preventing postherpetic neuralgia beyond its effect on reducing herpes zoster. Non-serious adverse events were more common among vaccine recipients than placebo recipients, but serious ones were rare. More well designed and specialised trials of vaccination for preventing postherpetic neuralgia are required.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Vaccination compared with placebo for preventing postherpetic neuralgia

Patient or population: people at risk for postherpetic neuralgia
Settings: clinical centres and other healthcare sites
Intervention: vaccination

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk vaccination				
Persistence of PHN among all subjects a numerical rating scale for pain[1] Follow-up: mean 3.13 years	**3 per 1000**	**1 per 1000** (1 to 2)	**RR 0.31** (0.18 to 0.54)	38501 (1 study)	⊕⊕⊕⊕ **high**	
Persistence of PHN among subjects developing herpes zoster a numerical rating scale for pain[1] Follow-up: mean 3.13 years	**84 per 1000**	**54 per 1000** (32 to 92)	**RR 0.64** (0.38 to 1.09)	957 (1 study)	⊕⊕⊕◯ **moderate**[2]	
Deaths among all subjects during the whole study clinical follow-up Follow-up: mean 3.13 years	**41 per 1000**	**41 per 1000** (37 to 45)	**RR 1.00** (0.91 to 1.1)	38546 (1 study)	⊕⊕⊕⊕ **high**	

Serious adverse events among subjects in the adverse event substudy clinical manifestations Follow-up: mean 3.13 years	**13 per 1000**	**20 per 1000** (13 to 29)	**RR 1.53** (1.03 to 2.25)	6616 (1 study)	⊕⊕⊕⊕ **high**

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Rated as 3 or more on the scale ranging from 0 (‘ ‘ no pain”) to 10 (‘ ‘ pain as bad as you can imagine”).
[2] Randomization was performed among all participants, but not among subjects developing herpes zoster.

BACKGROUND

Postherpetic neuralgia (PHN) is a painful condition that occurs following an acute herpes zoster infection. Recurrent herpes zoster, which is commonly referred to as 'shingles', is a neurocutaneous disease resulting from reactivation of latent varicella-zoster virus (VZV) infection within the sensory ganglia (Hope-Simpson 1965; Weller 1983). Unilateral radicular pain and a vesicular rash, usually limited to a single dermatome, are characteristic of herpes zoster (Gnann 2002).

The estimated lifetime incidence of herpes zoster is 10% to 20%. In young people the incidence is lower but it increases dramatically after 50 years of age. Some studies show that as many as 50% of individuals who live to 85 years of age will have herpes zoster at some time (Hope-Simpson 1965; Katz 2004). An age-related decrease in cell-mediated immunity is thought to account for the increased incidence in older age (Stankus 2000). Individuals with disease- or drug-related suppression of cellular immunity have a herpes zoster incidence 20 to 100 times greater than immunocompetent individuals. White ethnic background, psychological stress and physical trauma are also reported to be risk factors (Thomas 2004).

Postherpetic neuralgia is the most common complication of herpes zoster and most likely results from VZV-related damage to sensory ganglion neurons and axons and sensory neurons of the spinal tract (Gnann 2002; Mounsey 2005). Although PHN has been defined in various ways, we defined acute herpetic neuralgia as neuralgia within 30 days of rash onset, subacute herpetic neuralgia as between 30 and 120 days after rash onset, and PHN as persistent neuralgia at least 120 days after rash onset (Dworkin 1994; Desmond 2002). Pain often leads to depression, fatigue, insomnia, altered activities of daily living, and decreased socialisation. Individuals may also experience anorexia, physical inactivity and difficulty concentrating (Schmader 2002).

Treatment for pain is often initiated at the onset of the rash and may still be necessary months to years later. Treatments with possible efficacy for PHN include tricyclic antidepressants, gabapentin, pregabalin, opioids and topical lidocaine (Dubinsky 2004; Hempenstall 2005; Attal 2006), but two Cochrane systematic reviews concluded that there was insufficient evidence to recommend topical lidocaine (Khaliq 2007) or antidepressants (Saarto 2007) as first-line agents in the treatment of PHN, while another systematic review evaluating the efficacy of acupuncture for PHN is ongoing (Wang 2009). Further, in some patients PHN may persist for years and is often refractory to treatment (Dworkin 2003). Thus, the focus of research has turned to approaches that may prevent the development of PHN, and immunisation with a booster vaccine is a possible method. Our group has already systematically reviewed the effects of some possible measures for preventing PHN, but neither corticosteroids nor antiviral agents used acutely after zoster infection were proved effective (Li 2009; Chen 2010).

Over 40 years ago Hope-Simpson (Hope-Simpson 1965) suggested that a decline in VZV immunity is essential in the pathogenesis of herpes zoster and since then, the importance of T cell-mediated immunity has been increasingly recognised (Trannoy 2000). Researchers have found that VZV vaccination can enhance both VZV-specific, cell-mediated and humoral immunity (Berger 1985; Levin 1998). In addition, some clinical trials have prompted administration of zoster vaccine to reduce the burden and incidence of herpes zoster and PHN in older individuals (Hornberger 2006; SPS 2005).

A herpes zoster vaccine (shingles vaccine) (Zostavax, Merck), containing a live, attenuated VZV strain with at least 14-times the potency of varicella vaccine, was licensed in the United States by the Food and Drug Administration (FDA) in May 2006 for use in adults aged 60 years or older. Then, in 2008, the Advisory Committee on Immunization Practices (ACIP) recommended routine vaccination for preventing herpes zoster and its sequelae in people over 60 without contraindications to vaccination, but they specified that the zoster vaccine was not indicated to prevent persons with acute zoster from developing PHN (Centers for Disease Control and Prevention 2008).

The Shingles Prevention Study, a randomised, double-blind, placebo-controlled trial, was conducted to evaluate the efficacy of the zoster vaccine in preventing herpes zoster and PHN. It found that vaccine markedly reduced the incidence of herpes zoster and PHN among adults 60 years of age or older (SPS 2005). According to this study, the vaccine seems to be both safe and effective. However, it excluded participants with prior herpes zoster or aged less than 60 years, and it was conducted only in the United States, so it cannot completely reflect the actual results of all populations at risk for PHN. Therefore, this review aims to investigate systematically the efficacy and safety of vaccination in preventing PHN.

OBJECTIVES

The objective of this review was to investigate the efficacy and safety of vaccination in preventing PHN.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised trials (RCTs) (blinded and unblinded) were eligible for this review, irrespective of any language restrictions.

Types of participants

Any person who was administered the herpes zoster vaccine and control participants.

Types of interventions

The treatment comparisons investigated in this review are listed below.

1. VZV vaccination versus no vaccination.
2. VZV vaccination versus placebo.
3. VZV vaccination versus other interventions.

We excluded studies comparing different potencies of vaccine. We excluded studies without a valid control group, as the effect of the vaccine could not be assessed.

Types of outcome measures

Primary outcomes

The incidence of PHN at least four months after the onset of the acute herpetic rash.

We defined PHN as pain associated with herpes zoster, persisting or recurring at the site of shingles more than 120 days (four months) after the onset of herpes zoster rash.

Secondary outcomes

1. Pain severity measured by a validated scale, such as the 0 to 10 numerical rating scale (0 = no pain, 10 = worst possible pain) after four or six months (Cruccu 2004).
2. Adverse events within six weeks after vaccination. Adverse events were categorised as serious and non-serious. We defined serious events as those that are life-threatening, which require or prolong hospitalisation, cause death or result in persistent or significant disability. All other adverse events were considered non-serious.

Search methods for identification of studies

We searched the Cochrane Neuromuscular Disease Group Specialised Register (10 January 2011), the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 4, 2010 in the *Cochrane Library*), MEDLINE (January 1966 to December 2010), EMBASE (January 1980 to January 2011), LILACS (January 1982 to December 2010) and the Chinese Biomedical Retrieval System (January 1978 to December 2010). We reviewed the bibliographies of the RCTs identified, then we contacted the authors and known experts in the field and approached pharmaceutical companies to identify additional published or unpublished data. For the search strategies for MEDLINE, EMBASE, LILACS, CENTRAL and Chinese Biomedical Retrieval System see Appendix 1, Appendix 2, Appendix 3, Appendix 4 and Appendix 5.

We checked the references of published studies to identify additional trials, and also contacted the authors, known experts in the field and the pharmaceutical companies manufacturing the vaccine to identify additional published or unpublished data when necessary.

Data collection and analysis

Selection of studies

Two authors (Q Li and N Chen) independently scrutinised titles and abstracts identified from the searches. The two authors obtained full texts of all potentially relevant studies for independent assessment, and decided which trials might fit the inclusion criteria. When there were disagreements about the inclusion criteria, the two authors discussed the discrepancy carefully. A third author (L He) helped to arbitrate when no agreement was reached.

Data extraction and management

Two authors (Q Li and N Chen) independently extracted data, including the study name, type of design, study population size, duration, number of participant withdrawals, participants analysed in the different treatment groups, inclusion and exclusion criteria, intervention (route and dosage) and outcomes. We tried to obtain missing data from the study authors whenever possible. One author (N Chen) entered data into the Cochrane statistical software Review Manager (RevMan) 5 (RevMan 2008), and another one (Q Li) checked the accuracy. We used GradePro software to generate a 'Summary of findings' (SoF) table, which presented the quality of evidence for key outcomes including adverse events and the comparative risks between groups.

Assessment of risk of bias in included studies

We took several factors into account when we conducted the 'Risk of bias' assessment, such as the method of sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. We assessed these items using a domain-based evaluation according to the *Cochrane Handbook for Systematic Reviews of Interventions*, version 5.0.0 (Higgins 2008). We judged all included trials for each item using the following scale: 'Yes': low risk of bias, 'Unclear': unclear risk of bias, and 'No': high risk of bias.

Analyses

We undertook the analyses following the Cochrane Neuromuscular Disease Group guidelines. N Chen analysed the data using the RevMan software and reported the results according to Cochrane Collaboration criteria. For dichotomous variables, we

expressed the results as risk ratios (RRs) with 95% confidence intervals (CIs). For continuous variables, we compared means and calculated mean differences (MDs) with 95% CI.

We analysed data on an intention-to-treat basis. Therefore, we included all participants with available data in the analysis of the group to which they were allocated, regardless of whether or not they received the allocated intervention. If in the original reports participants were not analysed in the group to which they were randomised and there was sufficient information in the trial report, we attempted to restore them to the correct group. If data were insufficient, we contacted the study organisers.

Only one trial was included, so we did not perform heterogeneity or sensitivity investigations. If sufficient trials are available for analysis in future updates, we will undertake a sensitivity analysis on the basis of methodological quality and assess heterogeneity amongst trials by using the Chi^2 test with a 10% level of statistical significance ($P < 0.1$) and $I^2 > 50\%$ (Higgins 2002; Higgins 2003). If significant heterogeneity is present, we will undertake sensitivity analyses by repeating the calculation after omitting the trials which have low scores on individual quality items. We will use a fixed-effect model for meta-analysis unless we find unexplained heterogeneity, when we will use a random-effects analysis. For trials that are clinically heterogeneous or provide insufficient information for pooling, we will perform a descriptive analysis.

Subgroup analyses

We would have conducted subgroup analyses using different ages and different dosage of vaccine, if sufficient trials had been available:

1. 60 years of age or less versus more than 60 years of age;
2. one vaccine dose versus more than one dose.

RESULTS

Description of studies

See Tables: Characteristics of included studies and Characteristics of excluded studies.

After performing electronic searches using the strategy for each database, we found 511 possible references in MEDLINE, 762 in EMBASE, 50 in LILACS, 8 in the NMD register, 96 in CENTRAL and 33 in the Chinese Biomedical Retrieval System database. We also searched other resources, including the reference lists of published studies and relevant reviews, and information from known experts or pharmaceutical companies, but did not find any additional studies for assessment. We went through all the titles and abstracts and then identified 13 potentially eligible references, from which we excluded 10 after screening the full text. The reasons for exclusion included: measurement of immune response with no reference to the incidence or duration of PHN (Levin 1992; Sharp 1992; Levine 2000; Trannoy 2000; Macaladad 2007); a study of prevention of varicella or zoster with no reference to incidence or duration of PHN (Atsuko 2002; Mills 2010); and lack of comparison group (other approaches or placebo) (Levin 1998; Stephen 2007; Gilderman 2008).

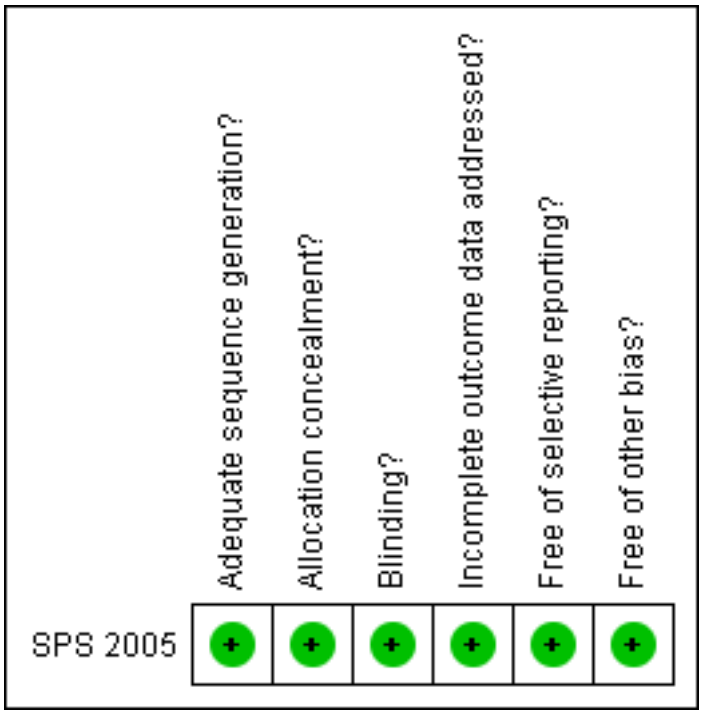
Only the Shingles Prevention Study (SPS 2005) with a total of 38,546 participants was identified as a true RCT and fulfilled our inclusion criteria; all three references were reports of this study.

The Shingles Prevention Study was a large randomised, placebo-controlled, double-blind, multicentre (22 sites) trial conducted by the Shingles Prevention Study Group in the United States. Sample size was estimated in the protocol using a herpes zoster incidence of 3/1000 person-years in individuals aged $\geq$ 60 years, with a loss to follow-up of 10% of subjects annually. A total enrolment of 37,500 subjects was planned, which was achieved in the study. Eligible subjects had either a history of varicella or had resided in the continental United States for at least 30 years, since more than 90% of adults in this area have serologic evidence of VZV infection and are at risk for herpes zoster while varicella is less common in tropical climates (Choo 1995; Gnann 2002). Those with a prior history of herpes zoster (shingles) or prior receipt of varicella vaccine, and those who were immunocompromised or unable to adhere to the study protocol were excluded. The median age of enrolled participants was 69 years and 41.0 percent were female. Participants were randomised in a 1:1 ratio to receive either a single dose of zoster vaccine (Zostavax) (n = 19,270) or placebo (n = 19,276) and were followed for a mean period of 3.1 years for development of PHN as the secondary endpoint.

Risk of bias in included studies

The only included study was a randomised, placebo-controlled, double-blind, multicentre trial, and a detailed description of the methods used in this study is provided in the Supplementary Appendix of the original article (SPS 2005; www.nejm.org). The relevant professional departments approved and monitored the study. For a summary of risk of bias assessments see Figure 1.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

In the included study, subjects were randomised in a 1:1 ratio to receive vaccine or placebo. Eligible subjects were sequentially assigned an allocation number in numerical order from the allocation schedules provided by the Cooperative Studies Program Coordination Center. Randomisation was stratified by site and by age group: 60 to 69 years and 70 years and over. Randomisation numbers were assigned sequentially within each age stratum at each participating site as subjects were enrolled. Sequence generation and allocation concealment were performed in this trial. As a result, the analysis of the study participants at baseline showed that the demographic characteristics of the two study groups were similar.

Blinding

Both zoster vaccine and placebo were lyophilised, but since the reconstituted zoster vaccine had a different appearance from the placebo, reconstitution and administration were performed by technicians who did not otherwise interact with subjects, evaluate outcomes or adverse events, answer the telephone, or enter study data. All other study personnel and the subjects were blinded to study treatment assignments.

Incomplete outcome data

Follow-up was well completed by an interactive Automated Telephone Response System (ATRS) and the local study site. The mean duration of herpes zoster surveillance was 3.13 years (median 3.12 years; range 1 day to 4.90 years). Only 0.6% of participants withdrew from the study or were lost to follow-up; 4.1% died during the study, with no difference between the groups.

It was specified in the protocol that if a subject was not contacted during the follow-up, at the end of the study he/she would be asked to report any previously unreported episodes of herpes zoster. This could have been a limitation for recording all of the incidences of herpes zoster or PHN and the details of duration and severity. However, closeout interviews did not identify any previously unreported cases of herpes zoster.

Selective reporting

We obtained the protocol for this trial from a FDA clinical briefing document for Zostavax (Rohan 2005). All the endpoints and outcomes specified in the protocol, such as herpes zoster burden of illness, incidence of PHN, incidence of herpes zoster, duration and severity of herpes zoster and substantial activities of daily living interference (ADLI), were reported in the published article.

Vaccine safety, including numbers and types of all adverse events and numbers and percentages of deaths, have also been reported.

Other potential sources of bias

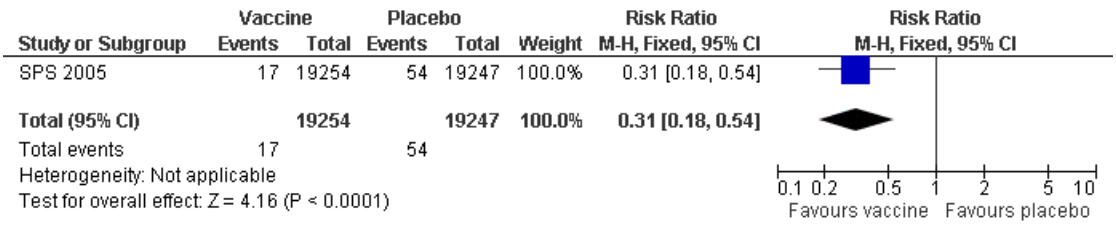
Pain management, including antiviral drugs, opioids and other various medications, was not specified by the study protocol, but it was offered to subjects with clinically diagnosed herpes zoster. This is a potential source of bias, although the authors claimed that differences in the use of pain medication did not inflate the estimates of vaccine efficacy.

Effects of interventions

See: **Summary of findings for the main comparison** Vaccination compared with placebo for preventing postherpetic neuralgia

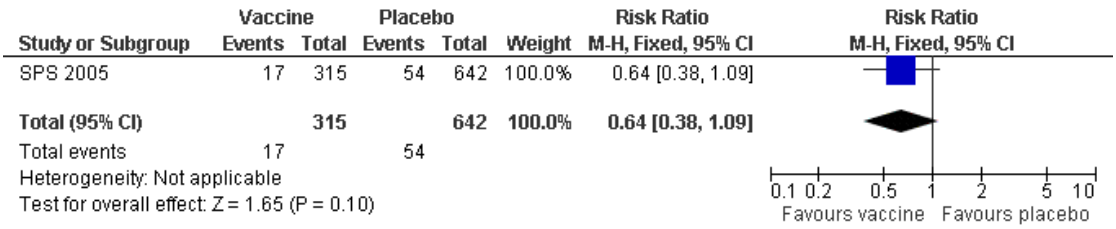
Vaccine efficacy for preventing herpes zoster compared with placebo was the primary outcome evaluated in SPS 2005. As a secondary outcome, a total of 71 cases of PHN developed among participants; 17 in the vaccine group and 54 in the placebo group (0.29 versus 0.93 cases per 1000 person-years, respectively; P < 0.001). PHN was defined as the pain and discomfort associated with herpes zoster that was rated as 3 or more on a scale ranging from 0 ("no pain") to 10 ("pain as bad as you can imagine"), persisting or appearing more than 120 days after the onset of herpes zoster rash. Overall, the zoster vaccine reduced the incidence of PHN significantly (RR 0.31, 95% CI 0.18 to 0.54) (Analysis 1.1; Figure 2); the number of people experiencing PHN decreased from about 3 per 1000 people to 1 per 1000 people (Summary of findings for the main comparison). The investigators also reported significant reductions in the incidence of PHN in the vaccine group compared with that in the placebo group, when the participants were stratified according to sex or age (60 to 69 years or ≥70 years old). When the definition of PHN was changed from 30 days to 182 days of pain following rash onset, the vaccine efficacy for PHN did not change appreciably. In a time-to-event analysis, the incidence rates of PHN remained significantly lower in the vaccine group than in the placebo group at up to five years follow-up (SPS 2005). Consequently, significant efficacy with respect to the incidence of PHN was demonstrated, regardless of how PHN was defined, with a trend toward greater efficacy for PHN of longer duration.

Figure 2. Forest plot of comparison: 1 Incidence of PHN, outcome: 1.1 Vaccine group versus placebo group.



However, since the incidence of herpes zoster was significantly different between groups, we evaluated the efficacy of the vaccine in preventing PHN among patients who developed herpes zoster. Among the 315 patients who developed herpes zoster in the vaccine group, there were 17 cases of PHN, while in the 642 participants who developed herpes zoster in the placebo group, 54 developed PHN. The incidence of PHN was 5.40% in the vaccine group and 8.41% in the placebo group (RR 0.64, 95% CI 0.38 to 1.09), which was not a significant difference (Analysis 2.1; Figure 3; Summary of findings for the main comparison).

Figure 3. Forest plot of comparison: 2 Incidence of PHN in subjects developed herpes zoster, outcome: 2.1 Vaccine group versus placebo group.



Pain severity was measured in the Shingles Prevention Study, using the 0 to 10 visual analogue rating scale mentioned above; however, no detailed data for zoster-associated pain, especially PHN, could be obtained from any version of the study. Thus, the efficacy of vaccination cannot be evaluated using one of the prespecified secondary outcomes, namely pain severity four or six months after the zoster onset.

In the Shingles Prevention Study all adverse events that occurred within 42 days of vaccination were recorded, and an adverse event substudy was carried out, which involved 3345 participants who received vaccine and 3271 who received placebo. Overall, in the 42 days post injection, similar types and low numbers (both 1.4%) of serious adverse events occurred in both groups. During the whole study, a similar number of deaths occurred in vaccine and placebo groups (both 4.1%) (Summary of findings for the main comparison). Varicella-like rash, a non-serious adverse event, was more common in the vaccine group than in the placebo group. For rashes at the injection site, the difference in risk was significant (0.1% versus 0.04%, P < 0.05) while insignificant at other sites (0.1% versus 0.1%, P > 0.05) (SPS 2005). In the safety substudy, however, rates of all kinds of adverse events and serious adverse events were both significantly higher in the vaccine group (RR 1.69, 95% CI 1.60 to 1.79) than the placebo group (RR 1.53, 95% CI 1.03 to 2.25) (Analysis 3.1; Figure 4; Analysis 3.2; Figure 5; Summary of findings for the main comparison). The incidence of serious adverse events was low (1.91% and 1.25% for each group) and the authors claimed that no clinically meaningful differences were found between groups according to a subject-to-subject review of serious adverse events (SPS 2005). Adverse events at the injection site were more common among vaccine recipients than placebo recipients (P < 0.05) as well as among the total subjects, but they were mild and resolved in a few days. Furthermore, over the entire study period no Merck/Oka vaccine DNA strain was detected in any participants with confirmed herpes zoster, which indicated that vaccination did not cause or induce herpes zoster. Zoster vaccine used in the Shingles Prevention Study was considered safe for its recipients.

Figure 4. Forest plot of comparison: 3 Adverse events within 6 weeks after vaccination, outcome: 3.1 All adverse events.

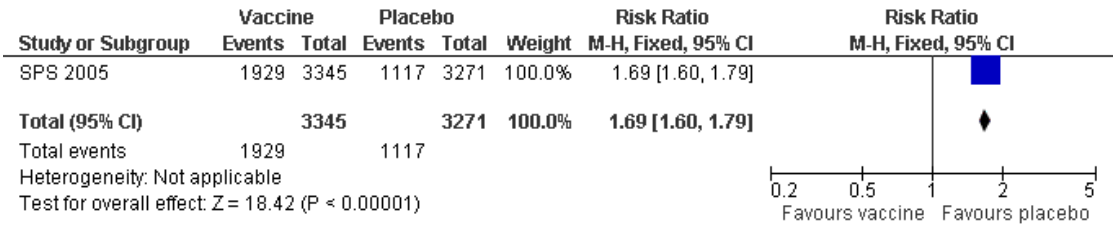
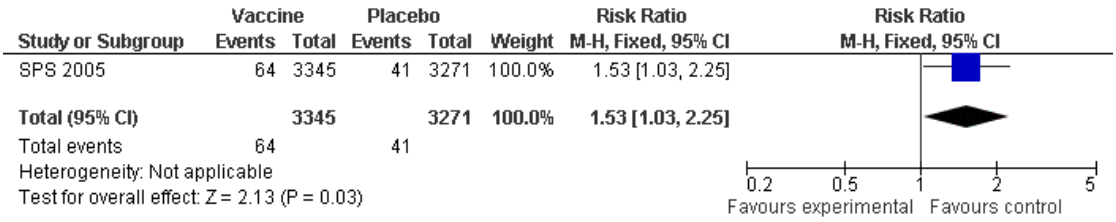


Figure 5. Forest plot of comparison: 3 Adverse events within 6 weeks after vaccination, outcome: 3.2 Serious adverse events.



Neither of the subgroup analyses specified in the protocol could be undertaken (between younger and older than age 60 and between low and high dosage), because all participants were 60 years of age or older and received a single dose of zoster vaccine or placebo.

DISCUSSION

The zoster vaccine (Zostavax), a live attenuated Oka/Merck VZV vaccine, essentially the same as the widely used varicella vaccine but with a much more potent formulation, is a new approach used to prevent herpes zoster and postherpetic neuralgia (PHN). It has been licensed by the FDA (FDA: Product Approval Information 2006) and recommended by the Advisory Committee on Immunization Practices (ACIP), but there are still only a few studies in this field. This systematic review summarises the evidence from randomised controlled trials (RCTs) of vaccination in preventing PHN.

Summary of main results

We found only one RCT concerning prevention of PHN by vaccination to fulfil the inclusion criteria. The Shingles Prevention Study (SPS) was a well designed, multicentre RCT with a large sample of subjects. It established the efficacy and safety of the zoster vaccine against herpes zoster. Its outcomes showed that the vaccine reduced the occurrence of herpes zoster in elderly adults and was associated with low rates of serious adverse events and generally mild local site reactions. There is high quality evidence that vaccination against herpes zoster reduces PHN in all participants vaccinated. However, defined by a cutoff of 120 days after rash onset, the incidence of PHN in participants who had been vaccinated but developed herpes zoster was not significantly reduced (8.41% in the placebo group compared to 5.40% in the vaccine group (P = 0.10)). It appeared that the major effect in the SPS was the decrease in the incidence of herpes zoster, and that the vaccine had minimal efficacy in reducing the incidence of PHN beyond its efficacy in preventing herpes zoster. We have graded the evidence here as moderate as we have derived this from the trial data.

Overall completeness and applicability of evidence

Although it had a large sample size and was well designed, the single trial we identified provided evidence only that vaccination reduces the incidence of herpes zoster. It did not support an additional effect on reducing PHN beyond this effect. Quantitative pain levels were not assessed in participants with PHN.

Furthermore, most of the participants (95.4%) in this study were white, so we could not draw any conclusion about the vaccine's effect in other ethnic groups. The efficacy of the zoster vaccine in individuals who are immunocompromised or have already had herpes zoster or who are younger than 60 years of age is unknown because these groups were excluded from the included study. The modified intent-to-treat (MITT) trial population excluded subjects who developed herpes zoster in the first 30 days following vaccination, mainly to avoid any impact on the investigation of the incidence of herpes zoster. However, we considered this to be missing data on vaccine efficacy for PHN. We attempted without success to find sufficient information on these excluded subjects to restore them to analysis.

Potential biases in the review process

We attempted to control for potential bias by using well defined systematic searches and avoiding limitations by publication status or language. Despite this, all possibly potentially eligible articles were written in English, so publication and retrieval biases might still be considered.

Agreements and disagreements with other studies or reviews

The United States FDA approved herpes zoster vaccine for preventing shingles in people older than 60 years, but pointed out that the efficacy of the vaccine in preventing PHN beyond the efficacy of the vaccine in reducing the incidence of herpes zoster was minimal through analysis of the SPS data (VRBPAC 2005). ACIP also specified that zoster vaccination was ineffective in preventing

persons with acute zoster from developing PHN or treating established PHN (Centers for Disease Control and Prevention 2008). Stephen et al. conducted a study involving 185 persons aged 50 to 59 years and evaluated the safety and tolerability of different doses of the zoster vaccine (62 received the standard potency, while 123 received high potency) (Stephen 2007). Both potencies were approved as safe and well tolerated. Another study (Macaladad 2007) investigated the safety and immunogenicity of a zoster vaccine in 21 healthy adults and reached the conclusion that the vaccine was generally well tolerated in healthy adults 30 years of age or older. Both the studies were in agreement with our included study (SPS 2005) in terms of the safety of the zoster vaccine .

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient direct evidence to prove the efficacy of vaccination for the prevention of PHN, although herpes zoster virus vaccine may be efficacious and safe for the prevention of herpes zoster and thus reduce PHN incidence in all vaccinated adults aged 60 years or older.

Implications for research

There is a need for further RCTs, especially those that provide data regardless of the incidence of herpes zoster, to investigate vaccination for the prevention of PHN. The inclusion criteria should be set to involve participants at risk for PHN, regardless of age, ethnicity or gender, and with or without a history of herpes zoster. If necessary and safe enough, vaccine may be given to patients with acute zoster to investigate its efficacy for preventing PHN directly.

ACKNOWLEDGEMENTS

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* Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *New England Journal of Medicine* 2005;**352**(22):2271–84.
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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

SPS 2005

Methods	A randomised, placebo-controlled, double-blind multicentre (at 22 sites) trial
Participants	A total of 38,546 subjects were enrolled (the median age was 69 years; more than 6% were age ≥ 80 years) All subjects were required to be immunocompetent without a prior history of herpes zoster or receipt of varicella vaccine, and to have a history of varicella or residence in the United States for at least 30 years
Interventions	Subjects were randomised to receive either a single dose of zoster vaccine (Zostavax) (a subcutaneous injection of 0.5 ml of the investigational live attenuated Oka/Merck VZV vaccine, with a median potency of 24,600 plaque-forming units) (n = 19,270) or placebo (n = 19,276)
Outcomes	1. Burden of illness from herpes zoster. 2. Incidence of PHN. 3. Incidence of herpes zoster
Notes	A 90-day cutoff defining PHN was used in this trial and corresponding data were analysed, but data on PHN defined by different cutoff (30 to 182 days after rash onset) were recorded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Allocation numbers in numerical order from the allocation schedules provided by the Cooperative Studies Program Coordination Center were used
Allocation concealment?	Low risk	Each study site received randomly ordered vials of VZV and placebo in separate boxes for each age stratum
Blinding? All outcomes	Low risk	Since the reconstituted VZV had a different appearance from the placebo, reconstitution and administration were performed by technicians who did not otherwise interact with subjects, evaluate outcomes or adverse events, answer the telephone, or enter study data. All other study personnel were blinded to study treatment assignments
Incomplete outcome data addressed? All outcomes	Low risk	Missing data were equal between groups, and efficacy analyses were performed using the intention-to-treat population

SPS 2005 (*Continued*)

Free of selective reporting?	Low risk	Outcomes listed in the methods section were all reported
Free of other bias?	Low risk	No other potential bias was found

PHN: postherpetic neuralgia; VZV: varicella zoster vaccine

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Atsuko 2002	Refers to vaccination for preventing for herpes zoster in haematopoietic cell transplant recipients but no reference to PHN
Gilderman 2008	Compares different formulations of vaccine (a refrigerator-stable formulation versus a frozen formulation) without comparison with other approaches or placebo
Levin 1992	Investigates immune response of vaccines, but does not refer to incidence or duration of PHN
Levin 1998	Investigates VZV-specific T cell immunity, so all participants received a vaccine for more than 6 years, without any comparison
Levine 2000	Investigates immune response of vaccines, but no reference to incidence or duration of PHN
Macaladad 2007	Investigates safety and immunogenicity of VZV, but no reference to incidence or duration of PHN
Mills 2010	Investigates safety, tolerability and immunogenicity of zoster vaccine, but no reference to incidence or duration of PHN
Sharp 1992	Investigates immune response of vaccines, but no reference to incidence or duration of PHN
Stephen 2007	Compares different potencies of vaccine without comparison with other approaches or placebo
Trannoy 2000	Investigates the efficacy of vaccine in terms of immune response, but no reference to incidence or duration of PHN

PHN: postherpetic neuralgia; VZV: varicella zoster vaccine

DATA AND ANALYSES

Comparison 1. Incidence of PHN

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaccine group versus placebo group	1	38501	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.18, 0.54]

Comparison 2. Incidence of PHN in subjects developed herpes zoster

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaccine group versus placebo group	1	957	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.38, 1.09]

Comparison 3. Adverse events within six weeks after vaccination

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All adverse events	1	6616	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [1.60, 1.79]
2 Serious adverse events	1	6616	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.03, 2.25]

Analysis 1.1. Comparison 1 Incidence of PHN, Outcome 1 Vaccine group versus placebo group.

Review: Vaccination for preventing postherpetic neuralgia

Comparison: 1 Incidence of PHN

Outcome: 1 Vaccine group versus placebo group

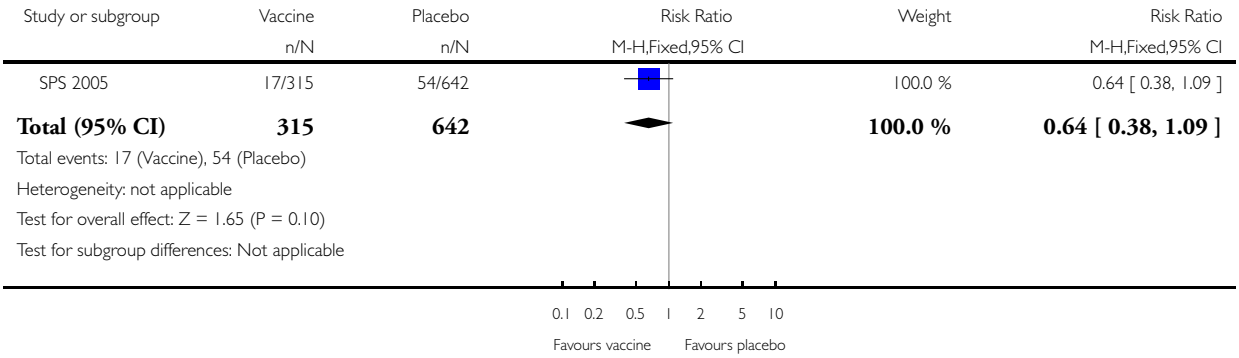
Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
SPS 2005	17/19254	54/19247		100.0 %	0.31 [0.18, 0.54]
Total (95% CI)	**19254**	**19247**		**100.0 %**	**0.31 [0.18, 0.54]**
Total events: 17 (Vaccine), 54 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.16 (P = 0.000032)					
Test for subgroup differences: Not applicable					

Analysis 2.1. Comparison 2 Incidence of PHN in subjects developed herpes zoster, Outcome 1 Vaccine group versus placebo group.

Review: Vaccination for preventing postherpetic neuralgia

Comparison: 2 Incidence of PHN in subjects developed herpes zoster

Outcome: 1 Vaccine group versus placebo group



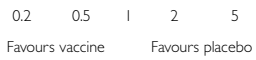
Analysis 3.1. Comparison 3 Adverse events within six weeks after vaccination, Outcome 1 All adverse events.

Review: Vaccination for preventing postherpetic neuralgia

Comparison: 3 Adverse events within six weeks after vaccination

Outcome: 1 All adverse events

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
SPS 2005	1929/3345	1117/3271		100.0 %	1.69 [1.60, 1.79]
Total (95% CI)	**3345**	**3271**		**100.0 %**	**1.69 [1.60, 1.79]**
Total events: 1929 (Vaccine), 1117 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 18.42 (P < 0.00001)					
Test for subgroup differences: Not applicable					



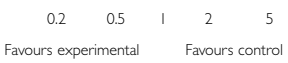
Analysis 3.2. Comparison 3 Adverse events within six weeks after vaccination, Outcome 2 Serious adverse events.

Review: Vaccination for preventing postherpetic neuralgia

Comparison: 3 Adverse events within six weeks after vaccination

Outcome: 2 Serious adverse events

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
SPS 2005	64/3345	41/3271		100.0 %	1.53 [1.03, 2.25]
Total (95% CI)	**3345**	**3271**		**100.0 %**	**1.53 [1.03, 2.25]**
Total events: 64 (Vaccine), 41 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.13 (P = 0.033)					
Test for subgroup differences: Not applicable					



APPENDICES

Appendix 1. MEDLINE OvidSP search strategy

1 randomized controlled trial.pt.
2 controlled clinical trial.pt.
3 randomized.ab.
4 placebo.ab.
5 drug therapy.fs.
6 randomly.ab.
7 trial.ab.
8 groups.ab.
9 or/1-8
10 exp animals/ not humans.sh.
11 9 not 10
12 exp Herpes Zoster/pc
13 herpes zoster.ti,ab.
14 shingles.mp.
15 chickenpox/pc
16 Neuralgia, Postherpetic/pc
17 (postherpetic neuralgia or post-herpetic neuralgia).tw.
18 (postherpetic pain or post-herpetic pain).tw.
19 PHN.tw.
20 or/12-19
21 exp Chickenpox Vaccine/
22 chickenpox vaccine$.tw.
23 Vaccines, Attenuated/
24 Herpesvirus 3, Human/
25 vzv vaccine.mp.
26 zoster vaccine.ti,ab.
27 or/21-26
28 11 and 20 and 27

Appendix 2. EMBASE OvidSP search strategy

1 crossover-procedure/
2 double-blind procedure/
3 randomized controlled trial/
4 single-blind procedure/
5 (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).tw.
6 or/1-5
7 exp animals/
8 exp humans/
9 7 not (7 and 8)
10 6 not 9
11 limit 10 to embase
12 Herpes Zoster/pc [Prevention]
13 Chickenpox/pc [Prevention]
14 shingles.mp.
15 herpes zoster.tw.
16 Postherpetic Neuralgia/pc [Prevention]
17 (postherpetic neuralgia or post-herpetic neuralgia).tw.
18 phn.mp.

19 or/12-18
20 Varicella Zoster Vaccine/
21 Chickenpox Vaccine/
22 Live Vaccine/
23 chickenpox vaccine$.tw.
24 zoster vaccine$.tw.
25 vzv vaccine.tw.
26 or/20-25
27 11 and 19 and 26

Appendix 3. LILACS search strategy

Herpes Zoster or shingles or chickenpox or Mh Neuralgia, Postherpetic or postherpetic neuralgia or post-herpetic neuralgia or postherpetic pain or post-herpetic pain or PHN [Words] and Chickenpox Vaccine or Mh Vaccines, Attenuated or attenuated vaccine or Mh Herpesvirus 3, Human or vzv vaccine or zoster vaccine [Words] and ((Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animals AND NOT (Ct humans and Ct animals)) OR (Pt clinical trial OR Ex E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh placebos OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR Mh research design) AND NOT (Ct animals AND NOT (Ct humans and Ct animals)) OR (Ct comparative study OR Ex E05.337$ OR Mh follow-up studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct animals AND NOT (Ct humans and Ct animals))) [Words]

Appendix 4. Cochrane Central Register of Controlled Trials search strategy

#1MeSH descriptor Herpes Zoster explode all trees
#2“herpes zoster”
#3shingles
#4MeSH descriptor Chickenpox, this term only
#5MeSH descriptor Neuralgia, Postherpetic, this term only
#6“postherpetic neuralgia” OR “post-herpetic neuralgia”
#7“postherpetic pain OR post-herpetic pain”
#8PHN
#9(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
#10MeSH descriptor Chickenpox Vaccine explode all trees
#11“chickenpox vaccine*”
#12MeSH descriptor Vaccines, Attenuated, this term only
#13MeSH descriptor Herpesvirus 3, Human, this term only
#14“vzv vaccine”
#15“zoster vaccine”
#16(#10 OR #11 OR #12 OR #13 OR #14 OR #15)
#17(#9 AND #16)

Appendix 5. Chinese Biomedical Retrieval System search strategy

(NB. all of the search terms were translated to Chinese terms when we conducted the searches)
1. herpes zoster
2. postherpetic neuralgia
3. PHN
4. shingle
5. 1-4/or
6. herpes
7. neuralgia
8. 6 and 7
9. 5 or 8
10.vaccine
11.vaccination
12.10-11/or
13.random
14.control
15.clinical trial
16.blind procedure
17.placebo
18.13-17/or
19.9 and 12 and 18

WHAT'S NEW

Last assessed as up-to-date: 9 January 2011.

Date	Event	Description
1 March 2011	Amended	Correction of typographical error in CENTRAL search strategy (no impact on results of search) and edits to search methods section

CONTRIBUTIONS OF AUTHORS

Ning Chen and Qifu Li performed the bibliographic searches, identified the studies, assessed their methodological quality, extracted the data, and Ning Chen produced the first draft of the review. Muke Zhou and Yun Zhang helped to perform the bibliographic searches, identified the studies and analysed the data. Li He and Dong Zhou assessed the methodological quality of the studies, checked the extracted data, and commented on all the draft manuscripts.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- Department of Neurology, West China Hospital, China.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we stated that we would include RCTs and quasi-RCTs. In the review we only included RCTs and excluded quasi-RCTs for higher reliability.

We have included a 'Summary of findings' table in the review; this table was generated in GradePro software and it presents the quality of evidence for some key outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

Herpes Zoster Vaccine [adverse effects; *therapeutic use]; Neuralgia, Postherpetic [*prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans